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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/284,683	06/24/1999	GREGOR CEVC	35946-701.831	2670

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EXAMINER	
KISHORE, GOLLAMUDI S	
ART UNIT	PAPER NUMBER
1612	
MAIL DATE	DELIVERY MODE
04/02/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/284,683	CEVC, GREGOR	
	Examiner	Art Unit	
	Gollamudi S. Kishore, Ph.D	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 February 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *106-110,112-118 and 120-123* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *106-110,112-118 and 120-123* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12-26-07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment dated 2-28-08 is acknowledged.

Claims included in the prosecution are 106-110, 112-118 and 120-123.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 116-118 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 106 recites the language 'consisting essentially of'; the dependent claim 116 which recites "vesicle further consists essentially of one or more consistency modifiers----" is inconsistent with the language in the parent claim.

Applicant's arguments have been fully considered, but are not persuasive. Applicant argues that the antioxidants and consistency modifiers in claim 116 do not materially affect the basic and novel characteristics of the vesicles. These arguments are not persuasive since according to claim 106, the essential components making up the vesicle are the phospholipids, NSAID and benzyl alcohol which is an antioxidant and therefore, any additional lipophilic antioxidant which is embedded in the lipid bilayer would change the characteristics of the bilayer and thus, changes the novel nature of the vesicle.

Claim Rejections - 35 U.S.C. § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 106-110, 112-118 and 120-123 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vyas (Journal o micro encapsulation, 1995) or Hayward (5,585,109) or Sheffield (4,937,254) in combination r Radhakrishnan (5,043,165), Edger (5,498,420) by themselves or together in further combination with Mezei (4,897,269).

Vyas discloses topical application of liposomes consisting essentially of PC and diclofenac in PBS, pH 7.4 (abstract, Table 1 formulation L1).

Hayward discloses liposomal formulations containing soy lecithin and salicylic acid and a method of delivery to the skin. The carrier material is polymethacrylate gel. The pH is 6.5 to 7.5. The composition further contains antioxidants and preservatives and hydrocolloids (columns 3-7). What is lacking in Hayward is the use of claimed antioxidants and Stabilizers.

Sheffield teaches a method of topical administration of liposomal formulations containing phosphatidylcholine and NSAID. The method of administration is topically and either internally or externally which implies skin. The composition further contains PBS and hydrocolloids (col. 3, lines 7-56; col. 6, line 15 through col. 7, line 12, Examples 13-15).

What is lacking in Vyas, Hayward or Sheffield is the inclusion of benzyl alcohol. Vyas and Sheffield also do not teach the use of unilamellar vesicles of instant sizes. Hayward is silent with respect to the nature of the liposomes.

Radhakrishnan while disclosing liposomal formulations teaches that multilamellar preparations can be treated to produce small unilamellar vesicles, large unilamellar vesicles or oligolamellar vesicles which are characterized by sizes in the 0.04-0.08 microns, 0.1 to 0.5 microns and mixed micron range. Radhakrishnan further teaches that the advantage of the suvs is the greater packing density of the liposomes at a mucosal surface and suvs are preferred for topical or nasal use (col. 7, line 45 through col. 8, line 14).

Edger while disclosing liposomal formulations for topical use teaches that from statistical point of view the interaction of small unilamellar vesicles with other cells is likely to be greater than that of multilamellar vesicles which facilitates the transfer of membrane constituents (col. 1, line 48 through col. 2, line 10).

Mezei while disclosing liposomal compositions teaches the addition of preservatives and antioxidants such as benzyl alcohol and tocopherol (abstract, Example 4 and col. 14, lines 42-63).

The use of small unilamellar vesicles of claimed sizes would have been obvious to one of ordinary skill in the art because of the advantages taught by Radhakrishnan and Edger. The addition of antioxidants and stabilizers in the compositions of Vyas or Hayward or Sheffield would have been obvious to one of ordinary skill in the art since such an addition would prevent oxidation of lipids and degradation by bacteria respectively as taught by Mezei. What is lacking in Hayward is the teaching of the use of synthetic phospholipid. However, since liposomes can be formed with either natural or synthetic phospholipids, it is deemed obvious to one of ordinary skill in the art to choose the desired source with a reasonable expectation of success. Hayward and Sheffield also lack the teaching of the application of the claimed amount of the liposomes on the skin surface. However, since the amount applied depends upon the condition to be treated and the severity of the condition, it is deemed obvious to one of ordinary skill in the art to manipulate this parameter to obtain the best possible results.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that Vyas uses multilamellar vesicles; applicant further argues that Vyas states that for ultrasound application, drug release was increased and found to be dependent on liposomal size and percent drug entrapment and concludes that liposomal formulation having the largest sizes showed the most effectiveness. This argument is not persuasive since at the same location, Vyas teaches "The increased release is probably due to breaking of lamellae on sonication". It is well-known in the art that small unilamellar vesicles are produced from multi-lamellar vesicles by sonication. Furthermore, Vyas's teachings pertain to when ultrasound is used. However, it would

have been obvious to one of ordinary skill in the art to use small unilamellar vesicles as opposed to multilamellar vesicles when the administration is topical, without ultrasound, because of the advantages taught by Radhakrishnan and Edger.

Applicant argues that Sheffield teaches away from the administration of vesicles that have a size of 50-500 nm since Sheffield states that the use of MLVs of comparatively large size (e. g. 1 to 5 microns appear to be preferable in order to increase the dwell time of the vesicles containing the NSAIDs in the peritoneal cavity. These arguments are not persuasive since instant claims are composition claims and the teachings of Sheffield pertain to the compositions when applied to peritoneal cavity and not when applied topically or mucosally. When the administrations are either topical or mucosal, the advantages taught by Radhakrishnan and Edger are still applicable. The examiner has already addressed applicant's arguments of Hayward's teaching away from the use of salts of NSAIDs in the previous action. In response to the examiner's position, applicant argues that pKa of most NSAIDs is between 3 and 5 as evident from Bosck et al, and based on the Henderson-Hasselback equation, an NSAID whose pKa=5 will be present in at least some salt from, if not predominantly in the salt form even at pH 3. This argument is not persuasive since 'most of NSAIDs' does not mean all of the NSAIDs behave the same way and all of them are weak acids. The reference submitted does not say anything about salicylic acid taught by Hayward. Furthermore, as applicants themselves state that instant composition contains even NSAID not in a salt form.

5. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S. Kishore, Ph.D whose telephone number is (571) 272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Krass Frederick can be reached on (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Gollamudi S Kishore, Ph.D/
Primary Examiner, Art Unit 1612

GSK